REMARKS

Utility

Claims 1-5 were rejected under 35 U.S.C § 101 on the assertion that they lack utility. The Examiner asserts that the data set forth in the specification are preliminary at best because the specification does not teach the expression of the PRO1069 polypeptide nor any particular biological activity of the polypeptide. The Declaration of J. Christopher Grimaldi was considered to be unpersuasive. Hu et al. was cited as teaching that, for genes displaying a 5-fold change or less in tumors compared to normal tissue, there was no evidence of a correlation between altered gene expression and a known role in the disease.

The second Declaration of J. Christopher Grimaldi and the Declaration of Dr. Paul Polakis were also found to be unpersuasive. With respect to Applicants' arguments regarding the Zhigang et al. reference the Examiner asserts that Zhigang et al. does show protein expression but that the experiments were carried out to demonstrate this. The Examiner asserts that Zhigang demonstrates that one needs to actually determine the expression of the protein to be sure of expression.

Meric et al. was cited as teaching that, in addition to variations in mRNA sequences that increase or decrease translational efficiency, changes in the expression or availability of components of the translational machinery (i.e., over-expression of eIF4E, eIF4G, eIF-2a, eIF-4A1, etc.) as well as activation of translation through aberrantly activated signal transduction pathways also effect the rate of translation in cancerous cells. In addition, the Examiner asserts that Meric et al., is in agreement with Alberts and Lewin, acknowledges that gene expression is quite complicated and is regulated at the level of mRNA stability, mRNA translation and protein stability. According to the Examiner, Meric goes on to indicate that the components of the translation machinery and signal pathways involved in the activation of translation initiation represent good targets for cancer therapy (see pages 975-976).

Jang was cited as teaching that further research would be required to determine if a correlation between mRNA and protein levels actually exists. Gygi et al., Haynes et al., and Hanash were cited as indicating that there was no correlation between mRNA and polypeptide levels.

With respect to the Orntoft et al. reference, the Examiner asserts that the authors concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes but this analysis was not done for PRO1069. The Examiner also asserts that Hyman et al. and Pollack et al. also do not support utility of the claimed antibodies.

Utility – Legal Standard

As previously noted, according to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "to violate § 101 the claimed device must be

totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., 'question') the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

As previously noted, an Applicants' assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence,

or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.** The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies have utility as diagnostic tools for cancer, particularly kidney cancer. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1069 polypeptide is more highly expressed in normal kidney compared to kidney tumor;

2. Applicants assert that it is well-established in the art that a **change** in the level of mRNA for a particular protein, e.g. an increase, generally leads to a corresponding **change** in the level of the encoded protein, e.g. an increase;

3. Given Applicants' evidence that the level of mRNA for the PRO1069 polypeptide is increased in normal kidney tissue compared to kidney tumor, it is likely that the PRO1069 polypeptide is more highly expressed in normal kidney compared to kidney tumor;

4. Antibodies which bind to proteins which are differentially expressed in certain tumors are useful as diagnostic and therapuetic tools.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the reliability of the evidence reported in Example 18, and states that it provides no information regarding protein expression in tumor samples relative to normal samples;

2. The PTO asserts that it has provided numerous references which demonstrate that mRNA does not correlate with protein.

As detailed below, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.02 III B. First, the PTO has failed to offer any evidence to support its rejection of the data in Example 18 and the Declaration of Chris Grimaldi in support of these data. Second, Applicants submit that in general differential mRNA expression correlates with differential protein expression. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Applicants have established that the Gene Encoding the PRO1069 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

The Examiner asserts that the Grimaldi declarations state that Example 18 showed mRNA expression but do not state that the protein was expressed.

As previously noted, the data in Example 18 demonstrates that the mRNA encoding PRO1069 is more highly expressed in normal kidney compared to kidney tumor. In support of this position, Applicants have previously submitted a copy of a first declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (first Grimaldi Declaration, Paragraph 7).

As Mr. Grimaldi states, "[i]f a difference is detected, this indicates that *the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic*

purposes, to screen samples to differentiate between normal and tumor." (first Grimaldi Declaration, Paragraph 7, emphasis added). The data presented in Example 18 show that the gene encoding PRO1069 is more highly expressed in normal kidney tissue compared to kidney tumor. As the first Grimaldi declaration indicates, the disclosed gene and its corresponding polypeptide and antibodies are therefore useful as diagnostic tools.

Applicants submit that the declaration is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). As discussed herein, the PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinion. Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no reason or evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept the statements in Mr. Grimaldi's Declaration.

Hu et al. was cited as teaching that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. As previously noted, in Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly,

Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a polypeptide that is 2-fold or more differentially expressed in tumors to be used as a diagnostic.

Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer or their corresponding proteins cannot serve as a molecular marker of cancer.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration previously submitted, establish that the mRNA encoding PRO1069 is more highly expressed in normal kidney tissue compared to kidney tumor. As Applicants explain below, it is more likely than not that the PRO1069 polypeptide is also differentially expressed and can be used to distinguish normal kidney tissue from kidney tumor.

Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a **change** in the level of mRNA for a particular protein, generally leads to a corresponding **change** in the level of the encoded protein. Given Applicants' evidence of differential expression of the mRNA for the PRO1069 polypeptide in kidney tumor, it is likely that the PRO1069 polypeptide is differentially expressed and can be used as a diagnostic tool.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (previously attached as Exhibit 1 to the Amendment filed August 13, 2004). As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted therewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D. (previously attached as Exhibit 3 to the Amendment filed August 13, 2004), an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994, herein after Cell 3rd) (previously submitted as Exhibit 1 with the Submission Filed with Request for Continued Examination filed March 18, 2005) and (4th ed. 2002, herein after Cell 4th) (previously submitted as Exhibit 1 with the Response to Final Office Action filed December 20, 2004, and as Exhibit 2 with the Submission Filed with Request for Continued Examination filed March 18, 2005), Genes VI, (Benjamin Lewin, Genes VI (1997)) (previously submitted as Exhibit 3 with the Submission Filed with Request for Continued Examination filed March 18, 2005), Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004 (previously submitted as Exhibit 2 with the Response to Final Office Action filed December 20, 2004, and as Exhibit 4 with the Submission Filed with Request for Continued Examination filed March 18, 2005) and Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002) (previously submitted as Exhibit 3 with the Response to Final Office Action filed December 20, 2004, and as Exhibit 5 with the Submission Filed with Request for Continued Examination filed March 18, 2005).

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

The Examiner asserts that the Declarations of Mr. Grimaldi and Dr. Polakis were not persuasive. According to the Examiner, Alberts and Lewin actually support the fact that further research would have to be carried out to determine if the polypeptide expression levels track with the expression levels of the corresponding mRNA. In particular, the Examiner asserts that Alberts and Lewin show that there are several levels that control gene expression both at the transcriptional (i.e., mRNA synthesis) and the translational (i.e., protein production) levels. The

Examiner maintains that one skilled in the art would not accept that increased mRNA levels directly correlate with the level of the corresponding polypeptide in view of the multitude of controls at the transcriptional and translational levels.

These arguments are not responsive. Applicants have already acknowledged that gene expression is regulated at numerous levels. However, as the supporting references and declarations Applicants have supplied make clear, regulation of mRNA levels is the predominant mechanism of control for the majority of genes.

With respect to Cell 3rd and Cell 4th, as previously noted, Figure 9-2 of Cell 3rd shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Cell 3rd provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Cell 3rd at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Cell 3rd at 453 (emphasis added). Thus, as established in Cell 3rd, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

As previously noted, in Cell 4th, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Cell 4th at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Cell 4th illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Cell 4th at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Cell 4th at 379 (emphasis added).

With respect to Lewin, as previously noted, Lewin states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot

inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added). Thus, it is clear from Lewin that protein expression is predominantly regulated at the point of transcription initiation.

The Examiner also asserts that, while Zhigang et al. does show protein expression, the experiments were carried out to demonstrate this. Thus, the Examiner maintains that Zhigang demonstrates that one needs to actually determine the expression of the protein to be sure of expression.

As previously noted, Zhigang reported that the correlation between mRNA expression and protein expression occurred in 93% of the samples tested. Applicants submit that there is no requirement to provide evidence sufficient to establish an asserted utility as a matter of statistical certainty. "Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true." M.P.E.P. at § 2107.02, part VII (2004) (emphasis in original, internal citations omitted). Accordingly, Applicants maintain that Zhigang is consistent with Applicants' position that, in general, differential mRNA expression leads to differential expression of the encoded polypeptide.

The Examiner asserts that Applicants have taken the statements by Meric out of context. According to the Examiner, Meric indicates most efforts have concentrated on gene expression at the mRNA level due to the advent of cDNA array technology, which facilitated this type of analysis. The Examiner asserts that Meric et al., in agreement with Alberts and Lewin, acknowledges that gene expression is quite complicated and is regulated at the level of mRNA stability, mRNA translation and protein stability and that Meric et al. goes on to indicate that the components of the translation machinery and signal pathways involved in the activation of translation initiation represent good targets for cancer therapy (see pages 975-976). The Examiner argues that, if it was the accepted understanding in the art that there is a direct correlation between mRNA levels and the level of expression of the encoded polypeptide, there would not be a need to target the translational machinery, unless of course the two are regulated separately.

As noted above, Applicants have already acknowledged that gene expression is regulated at numerous levels. However, as the supporting references and Declarations Applicants have supplied make clear, regulation of mRNA levels is the predominant mechanism of control for the majority of genes. Meric supports this assertion because "[t]he **fundamental principle** of molecular therapeutics in cancer is to exploit the **differences** in gene expression between cancer cells and normal cells." Meric *et al.* at 971 (emphasis added). The only reason mRNA is of any interest in studying the mechanism of cancer formation and growth is because mRNA encodes protein. If there were no general correlation between differences in mRNA and differences in protein, there would be no reason to study changes in mRNA. Furthermore, with respect to the Examiner's argument that there would be no need to target translational machinery for cancer therapy if there was a direct correlation between mRNA and protein, Applicants maintain that any point in the process of producing a polypeptide involved in cancer may be exploited as a target for therapy. The inclusion of translational machinery amongst the many potential target points does not indicate in any way that there is no correlation between mRNA levels and polypeptide levels.

The Examiner again refers to the statement in Jang et al. that "further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells." In response to Applicants' arguments, the Examiner recognizes that the statement by Jang does not mean that mRNA and protein levels were measured and found not to correlate, but asserts that this statement is an acknowledgement that further research would be required to determine if a correlation between mRNA and protein levels actually exists. The Examiner maintains that if it is established that the accepted understanding in the art that there is a direct correlation between mRNA levels and the level of expression of the encoded protein, Jang et al. would not state that "further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells."

As discussed above, Applicants do not assert that gene transcription is the only point of regulation. However, Applicants maintain that, as discussed above, gene transcription is the predominant point of regulation. Jang's statement is simply an indication that further research

could be performed to evaluate whether the genes of interest are regulated at the predominant point of regulation (transcription) or whether a less common point of regulation is utilized.

Gygi et al. is cited as stating "We found that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold." Haynes et al. is cited as teaching that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1).

Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi, p. 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. Id. Considering that Example 18 of the specification shows higher expression of PRO1069 mRNA in normal kidney compared to kidney tumor, Gygi actually provides strong evidence in support of a general correlation between mRNA and protein levels.

Haynes does not contradict the utility of the antibodies encompassed by the instant claims. Haynes is a review article dealing with the art of proteome analysis. The assertions in Haynes cited by the Examiner were made in an effort to identify shortcomings in the art of mRNA quantification to argue for "proteome analysis to become an essential component in the comprehensive analysis of biological systems." Haynes, p. 1863. Haynes studied 80 selected samples from *Saccharomyces cerevisiae*, and reported "a general trend but no strong correlation between protein and transcript levels (Fig. 1)." Id. However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured.

The 50-fold variation referred to by Haynes and cited by the Examiner, does not in any way show the absence of a correlation between mRNA and protein levels, but rather identifies the outer limits of variability in the authors' experiments. This variability may support the authors' assertion that the amount of a particular protein cannot accurately predict the particular level of the corresponding mRNA transcript, but it does not suggest an absence of a general correlation between mRNA and protein levels. Again, Applicants' utility is based on the differential expression of mRNA in normal skin tissue versus melanoma. Exact levels of

expression are irrelevant. Moreover, Gygi states that the high degree of variability seen at low levels of mRNA (shown in inset of Fig. 1, Haynes p. 1863) is due to the fact that "the magnitude of the error in the measurement of mRNA levels is inversely proportional to the mRNA levels." Gygi, p. 1727. Considering that PRO1069 mRNA has been shown in Example 18 of the specification to be more highly expressed in normal kidney than kidney tumor, the variability identified by Haynes is even less applicable to establishing the absence of a correlation between mRNA and protein levels in the instant case.

Hanash S. is cited as teaching that "There is a need to profile gene expression at the level of the proteome and to correlate changes in gene-expression profiles with changes in proteomic profiles. The two are not always linked-numerous alterations occur in protein levels that are not reflected at the RNA level". The Examiner also asserts that Hanash teaches that tumors are complex biological systems and no single type of molecular approach fully elucidates tumor behavior, necessitating analysis at multiple levels encompassing genomics and proteomics. According to the Examiner, it is not established in the art that the accepted understanding is that there is a direct correlation between mRNA levels and the level of expression of the encoded protein.

As discussed above, Applicants have already acknowledged that gene expression is regulated at numerous levels. However, as discussed above, the Declarations and supporting references supplied by Applicants make it clear that regulation of mRNA levels is the predominant mechanism of control for the majority of genes.

With respect to the Orntoft reference, the Examiner asserts that the authors appear to have looked at increased DNA content over large regions of chromosomes and compared that to mRNA and polypeptide levels from the chromosomal region. The Examiner asserts that Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. According to the Examiner, the instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region, which is highly amplified. The Examiner also maintains that Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes. The Examiner asserts that this analysis was not done for PRO1069 in the instant specification and

that it is not clear whether or not PRO1069 is in a gene cluster in a region of a chromosome that is highly amplified. According to the Examiner, the relevance of Orntoft et al. is not clear.

One would expect that amplification of chromosomal DNA would generally lead to an increase in mRNA transcribed from genes lying within the amplified region. In fact, as previously noted, Orntoft did look at mRNA and protein levels for individual genes located within amplified or deleted chromosomal regions and found that of the 40 proteins analyzed only one showed disagreement between transcript alteration and protein alteration (Orntoft, page 42). Applicants maintain that Orntoft's results demonstrate that, in general, a change in mRNA level results in a change in the level of the encoded polypeptide. Applicants maintain that this correlation is independent of whether the increase in mRNA levels is a result of increased transcription rate or a result of an increase in the copy number of the gene. Accordingly, it is immaterial whether or not the differential expression of mRNA encoding PRO1069 is a result of increased transcription rates or increased copy number. Regardless of the basis for increased PRO1069 mRNA levels, the general rule that a change in mRNA level leads to a change in the level of the encoded polypeptide still applies.

The Examiner asserts that Hyman et al. used the same CGH approach in their research as was used by Orntoft et al. and that less than half (44%) of highly amplified genes showed mRNA over-expression. The Examiner asserts that Hyman et al. did not investigate polypeptide levels. Applicants acknowledge that Hyman et al. did not evaluate polypeptide levels but reiterate that Hyman observed that "the results illustrate a considerable influence of copy number on gene expression patterns." Thus, Applicants maintain that Hyman et al. supports Applicants' position that an increase in gene copy number generally results in an increase in mRNA levels. However, as discussed above, whether or not the differential expression of mRNA encoding PRO1069 is a result of differences in gene copy number is immaterial since one would expect the differential mRNA expression to be accompanied by differential polypeptide expression in view of the general rule that differential expression of mRNA leads to differential expression of the encoded polypeptide.

The Examiner asserts that Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification and that the authors did not investigate polypeptide levels. According to the Examiner, because polypeptide levels were not

investigated, Pollack et al. does not support the asserted utility of the claimed invention. Applicants acknowledge that Pollack et al. did not evaluate polypeptide levels. However, Applicants reiterate that Pollack concluded "that on average a 2-fold change in copy number is associated with a corresponding 1.5-fold change in mRNA levels." (Pollack, abstract). Thus, Applicants maintain that Hyman et al. supports Applicants' position that an increase in gene copy number generally results in an increase in mRNA levels. However, as discussed above, whether or not the differential expression of mRNA encoding PRO1069 is a result of differences in gene copy number is immaterial since one would expect the differential mRNA expression to be accompanied by differential polypeptide expression in view of the general rule that differential expression of mRNA leads to differential expression of the encoded polypeptide.

The Examiner asserts that Orntoft et al., Hyman et al. and Pollack et al. did not report that their research was relevant to identifying probes that can be used as cancer diagnostics. Rather, the Examiner asserts that these three papers state that the research was relevant to the development of potential cancer therapeutics and imply that much further research was needed before such therapeutics were in readily available form.

Applicants note that the focus of the foregoing papers on therapeutics does not detract from the fact that polypeptides which are differentially expressed in cancer are useful as diagnostic tools. Applicants note that this position is supported by the Revised Interim Utility Guidelines promulgated by the PTO, which recognize that proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.)

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the

evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has not offered any arguments or cited any references that establish "that one of ordinary skill in the art would reasonably doubt" that the disclosed polypeptide is differentially expressed in certain tumors and that the claimed antibodies can be used as diagnostic and therapeutic tools. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed antibodies can be used as diagnostic or therapeutic agents for cancer, particularly kidney tumor.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the

PRO1069 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the mRNA for the PRO1069 polypeptide is more highly expressed in normal kidney compared to kidney tumor. These data are strong evidence that the PRO1069 gene and polypeptide are associated with kidney tumor. Thus, Applicants submit that they have provided evidence associating the PRO1069 gene and polypeptide with a specific disease. The asserted utility of the claimed antibodies as a diagnostic tool for cancer, particularly kidney tumor, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Conclusion

The PTO has challenged the reliability of the evidence reported in Example 18, and states that it provides no information regarding protein expression. The PTO also asserts that it has provided numerous references which demonstrate that mRNA does not correlate with protein.

Applicants have previously provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. Applicants maintain that the previously submitted second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels. The PTO has not offered any substantial reason or evidence to question these declarations and supporting references. One of skill in the art recognizes that polypeptides which are differentially expressed in certain cancers have utility as diagnostic or therapeutic tools for cancer. Applicants note that the claimed utility is specific because differential expression in kidney tumor is not a characteristic of proteins in general.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is <u>not</u> required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack

> utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Enablement

Claims 1-5 were rejected under 35 U.S.C. 112, first paragraph, on the assertion that, because the claimed invention is not supported by a substantial utility or a well-established utility, one skilled in the art would not know how to use the claimed invention.

As discussed above, the claimed antibodies do possess utility. Accordingly, one skilled in the art would know how to use them.

The Examiner asserts that, as discussed above with respect to the utility rejection, the art of Alberts, Lewin, Meric, Jang et al., Vallejo et al., Powell et al., Fu et al., Gygi et al., Haynes et al., Hanash S [a] and Hanash et al. [b] underscores the unpredictability in the art and discloses that the predictability of protein translation and its possible use as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Thus, the Examiner maintains that one of skill in the art could not predictably use the antibodies of the present claims as a diagnostic or therapeutic agent with a reasonable expectation of success.

As discussed above with respect to the utility rejection, Applicants maintain that, while there are some exceptions, in general differential expression levels of mRNA leads to differential protein expression levels. Accordingly, Applicants maintain that the references cited by the Examiner represent exceptions to the general rule.

Applicants further maintain that the use of antibodies as diagnostic tools involves routine methodology. Applicants reiterate that the implementation of routine techniques does not constitute undue experimentation. (See *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

In view of the foregoing, Applicants maintain that the specification enables one skilled in the art to make and use the claimed invention.

Priority

Priority is granted to PCT/US00/23328, filed 24 August 2000, as the disclosure of '328 is identical to the instant disclosure. However, the Examiner did not grant priority to USSN 09/380,137, PCT/US99/12252 and 60/088,740 on the assertion that these applications do not disclose the microarray assay upon which applicant relies for utility of the instantly claimed antibodies.

As an initial matter, Applicants would like to clarify that Example 18 used quantitative PCR analysis of a cDNA library to measure mRNA expression, not a microarray analysis. With respect to the priority date of the present application, Applicants note that this application is a continuation of, and claims priority to under 35 U.S.C. §120 to, U.S. Application 10/006867, filed 12/6/2001, which is a continuation of, and claims priority to under 35 U.S.C. §120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority to under 35 U.S.C. §120 to, U.S. Application 09/380137 filed 8/25/1999, which is the National Stage filed under 35 U.S.C. §371 of PCT Application PCT/US99/12252 filed 6/2/1999 which claims priority under 35 U.S.C. §119 to U.S. Provisional Application 60/088740 filed 6/10/1998.

Anticipation

Claims 1-2 and 4-5 were rejected under 35 U.S.C. 102(a) on the assertion that they are anticipated by Lal et al. (WO 00/00610, 1/6/2000, cited previously on PTO-892 mailed 4/15/2004). According to the Examiner, Lal et al. teach a polypeptide (SEQ ID NO:35), which is identical to the polypeptide of SEQ ID NO:50 and antibodies that bind the polypeptide.

Applicants note that in the present Office Action, the Examiner has withdrawn the previous rejection under 35 U.S.C. §103(a) based on the Lal in view of Queen et al. (See Office Action at pages 2-3 indicating that this rejection was withdrawn in view of Applicants'

arguments and the fact that Lal et al. do not teach the expression of the polypeptide or a function for the protein).

Applicants' previous arguments with respect to the Stemple Doctrine continue to apply to the current rejection under 35 U.S.C. §102(a). In particular, Applicants reiterate that Applicants first disclosed SEQ ID NO: 50 in U.S. Provisional Application Serial No. 60/088740, filed June 10, 1998. As previously noted, Lal's first provisional application relating to SEQ ID NO: 50, U.S. Provisional Application Serial No. 60/090,762, was filed June 26, 1998 (after Applicants' first application disclosing this sequence). Lal's provisional application did not contain any data correlating SEQ ID NO: 50 any particular disease or physiological function. W0 00/00610 discloses the sequence of SEQ ID NO: 50 and provides tissue distribution data for the corresponding transcript in Table 3, but does not correlate the protein with any particular disease by showing differential expression in diseased tissue relative to normal tissue and does not provide any other physiological function for the protein. In particular, Applicants maintain that the disclosure in Table 3 that the transcript is found in urologic tissue and is present to an equivalent degree in cancer, fetal tissue and inflammation (0.333 in each category) does not provide an association between the protein and any disease or physiological function.

Thus, Applicants maintain that they were in possession of so much of the invention as is disclosed in U.S. Provisional Patent Application Serial No. 60/090,762 and WO 00/00610 prior to the filing dates of each of these applications.

As previously noted, the well-established "Stempel Doctrine" stands for the proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he or she made that portion of the claimed invention that is disclosed in the prior art reference. (*In re Stempel*, 113 USPQ 77 (CCPA 1957)). In other words, a patent applicant need not demonstrate that he or she made the entire claimed invention in order to remove a cited prior art reference. He or she need only demonstrate prior possession of that portion of his or her claimed invention that is disclosed in the prior art reference and nothing more.

The Stempel Doctrine was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it in *In re Moore*, 170 USPQ 260 (CCPA 1971). More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the Examiner cited a

reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to the effective date of the cited prior art reference, he had not yet completed his "invention".

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established Stempel Doctrine to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (Id. at 267, emphasis added).

Thus, *In re Moore* confirms the Stempel Doctrine, holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either absent a utility or with a utility that is different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant need not demonstrate that he or she had discovered a patentable utility for the claimed chemical compound prior to the effective date of the prior art reference.

While these cases discuss the ability to effectively swear back of the cited reference by way of a 131 declaration, Applicants submit that the same reasoning applies here, where the application claims priority back to a disclosure that predates the cited reference. Because Applicants demonstrated, by means of the disclosure in their provisional application filed June 10, 1998, that they were in possession of so much of the claimed invention as is disclosed in U.S. Provisional Patent Application Serial No. 60/090,762 and WO 00/00610 prior to the filing

dates of these references, Applicants respectfully submit that these references are not available as prior art.

In addition, Applicants submit that the presently claimed invention antedates Lal's earliest priority date of June 26, 1998. The accompanying Declaration of Goddard et al., originally submitted in U.S. Patent Application Serial No. 10/063,555 (the corresponding application relating to the polypeptide recognized by the presently claimed antibodies), discussed in more detail below, establishes that the presently claimed subject matter was conceived prior to Lal's earliest priority date of June 26, 1998 and diligently reduced to practice thereafter. Thus, Applicants respectfully submit that the cited reference is not available as prior art.

Claims 1-2 and 4-5 were rejected under 35 U.S.C. 102(e) on the assertion that they are anticipated by Walker et al. (U.S. Patent 6,277,574 B1, 4/9/1999). The Examiner asserts that Walker et al. discloses a polypeptide (SEQ ID NO:11) that is identical to the polypeptide of SEQ ID NO:50 and monoclonal antibodies and antibody fragments that specifically bind the polypeptide.

As stated in the accompanying Declaration Under 37 C.F.R. §1.131, the presently claimed invention antedates the priority date of April 9, 1999 the PTO has asserted for Walker et al. The Declaration of Goddard et al. establishes that the presently claimed subject matter was conceived prior to the priority date of April 9, 1999, and diligently reduced to practice thereafter. Thus, Applicants respectfully submit that the cited reference is not available as prior art.

As set forth in 37 C.F.R. § 1.131, a patent applicant "may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based." *See also*, M.P.E.P. § 715. "The affidavit or declaration must state FACTS and produce such documentary evidence and exhibits in support thereof as are available to show conception and completion of the invention in this country ... at least conception being at a date prior to the effective date of the reference." *See* M.P.E.P. § 715.07 (emphasis in original). The showing of facts must be sufficient to show "conception of the invention prior to the effective date of the reference coupled with due diligence from prior to the reference date to a subsequent (actual) reduction to practice." *See id.*

The Declaration demonstrates that the claimed subject matter, more particularly antibodies which specifically bind to the polypeptide of SEQ ID NO: 50 was conceived by

Applicants prior to April 9, 1999. Furthermore, as evidenced by the Declaration and accompanying exhibits, Applicants exhibited diligence in reducing the subject matter of the claims to practice by performing various assays to confirm the function of the polypeptides recognized by the claimed antibodies. Therefore, Walker et al. is not available as prior art under 35 U.S.C. § 102(e).

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of these rejections.

Obviousness

Claims 1-5 were rejected under 35 U.S.C. 103(a) on the assertion that they are unpatentable over Walker et al. (U.S. Patent 6,277,57481, 4/9/1999) in view of Queen et al. (U.S. Patent 5,530,101). The Examiner maintains that it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a humanized antibody to the polypeptide of Walker et al. in view of Queen et al. The Examiner also asserts that one of ordinary skill in the art would have been motivated to produce a humanized antibody to the polypeptide of Walker et al. in view of Queen et al. because Walker et al. teach that the polypeptide of SEQ ID NO:50 (i.e., SEQ ID NO:11 of Walker et al) is associated with kidney disease and Queen et al. teaches humanized antibodies.

As discussed above, Applicants have demonstrated conception of the claimed invention prior to the April 9, 1999 date which the PTO asserts for the Walker reference along with diligence in reducing the invention to practice. Thus, Walker is not available as prior art. Applicants further maintain that the disclosure of humanized antibodies in Queen does not render the claimed antibodies obvious because there is no teaching or suggestion of antibodies which bind to the polypeptide of SEQ ID NO: 50 in Queen.

Conclusion

In view of the foregoing Applicants maintain that the application is in condition for allowance. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Oct. 12, 2005

By: Daniel Hart

Daniel Hart
Registration No. 40,637
Attorney of Record
Customer No. 30,313
(619) 235-8550

1948899
092205